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Direct Hydroheteroarylation of Ynamides with 2*H*-Tetrazoles: Regio- and Stereo-Selective Synthesis of (*Z*)-*α*-Tetrazol Enamides

Jiekun Zhu,[a] Qingbo Wang,[a] Xin Meng,*[a] Changyin Zhao,[a] Xuejun Sun,[a] Laijin Tian,[ab] Ziping Cao*[ab]

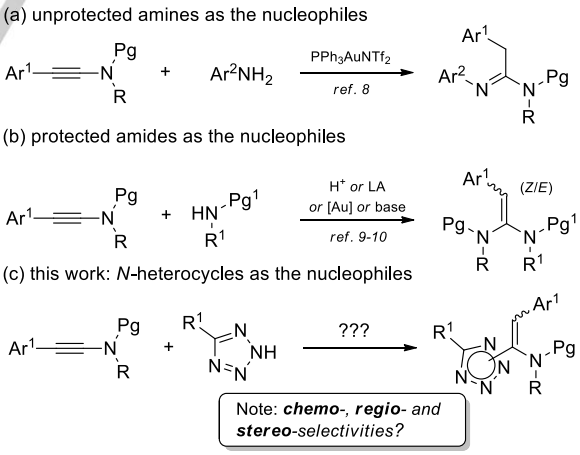
Dedication ((optional))

Abstract: We herein report the direct reaction of ynamides with 2*H*-tetrazoles could proceed under metal-free conditions to provide a variety of functionalized (*Z*)-*α*-tetrazol enamide products in high yields, including the *N*-2 and *N*-1 adducts that are easily separated. The reaction could undergo a key keteniminium ion intermediate, generated *in situ* from ynamides with acidic 2*H*-tetrazoles, leading to the formation of C-N bonds efficiently. The present reaction features simple experimental operations and mild reaction conditions, high chemo-, regio- and stereo-selectivities, and high reaction efficiencies. With the use of without any catalyst, the reaction protocol should facilitate the modification of tetrazole-containing molecules for the discovery of new potentially bioactive compounds.

Introduction

Ynamides are a class of especial alkyne derivatives that possess a functionalized nitrogen motif, and have attracted much attention in the organic synthetic community. As the useful and versatile building blocks for organic synthesis, ynamides could be converted into kinds of cyclic compounds by transition-metal-mediated cycloadditions and cycloisomerizations.[1-2] Moreover, ynamides are also excellent precursors for preparing functionalized enamide products by the addition reactions of nucleophiles. Usually, the additions are regioselective due to the electron-donating ability of the nitrogen. In 2003, Hsung reported an MgX_2-mediated *syn*-addition of HX onto the ynamides, leading to the formation of *α*-haloenamides efficiently.[3] After that, the synthesis of a variety of *α*-substituted enamides were achieved under Lewis or Brönsted acid-mediated conditions with the use of various nucleophilic reagents such as oxygen and sulfur nucleophiles, and electron-rich heteroarenes.[4-7] Notably, nitrogen-containing nucleophiles could participate in the addition reactions of ynamides. In 2009, Skrydstrup developed a gold-catalyzed hydroamination of ynamides for the synthesis of various amidine derivatives *via* the isomerization of enamide intermediates (Scheme 1a).[8] Thereafter, a wide range of enamide products have been obtained with protected amides as the nucleophiles by metal or acid catalysis (Scheme 1b), often having a mixture of *Z*/*E* isomers.[9] In addition, the reactions of cyclic carbamates or lactams with ynamides could lead to synthesis of bis-enamides in the presence of potassium phosphate (Scheme 1b).[10] Even so, the transformation of ynamides to various enamide derivatives under Lewis or Brönsted acid conditions is still rare, especially under extra catalyst-free conditions.

In this context, and following our ongoing interest in the transformations of alkynes into potentially useful skeletons,[11] we recently envisaged that the reaction of 2*H*-tetrazoles[12-13] with ynamides could proceed under metal- or acid-catalyzed conditions, leading to synthesis of novel *α*-tetrazol-substituted enamide products (Scheme 1c). These products could be useful in the field of medical chemistry, [14-15] and this study provides potentially a synthetic template of similar skeleton compounds for drug discovery programs. However, the reaction could raise three issues: 1) chemoselectivity of tetrazoles (*N*-1 and *N*-2 adducts); 2) regioselectivity of ynamide motif (*α*- and *β*-positions); and 3) stereoselectivity (*syn*- and *trans*-additions). Herein, we want to report the detailed results on the above-mentioned reaction (Scheme 1c).



Scheme 1. Reactions of Ynamides with Nitrogen-Containing Nucleophiles.

Results and Discussion

Our initial studies were carried out with ynamide **1a** and 5-methyl-2*H*-tetrazole **2a** as the model substrates (Scheme 2). In the presence of IPrAuCl/$AgNTf_2$ (5 mol%) with 1,2-dichloroethane (DCE) as the solvent at 80 ˚C for 2 h, the

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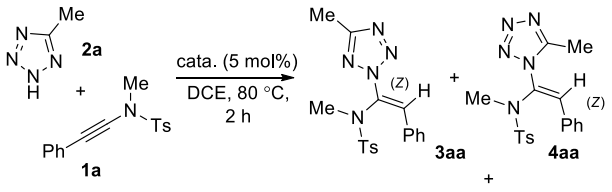
reaction could proceed smoothly to give three different products, which could be readily separated (R_f = 0.37 (**3aa**, 75%), 0.17 (**4aa**, 21%), 0.53 (**5**, 4%), PE/EA = 3/1). Notably, **3aa** and **4aa** possess complete regio-and stereo-selectivities determined by the ^{1}H NMR analysis of crude reaction mixture. The *Z*-configurations of the adducts were confirmed by single-crystal X-ray diffraction (Figure 1).[16] The further control experiments showed more hydrolyzed product **5** was provided with $AgNTf_2$ as the single catalyst. To our delight, the use of without catalyst led to the formation of adducts **3aa** and **4aa** in high efficiency. Meanwhile, the formation of product **5** was inhibited completely. These results could indicate that metal catalysts could not promote current transformation. The reaction could be catalysed by 2*H*-tetrazole **2a** which have an acidic proton on nitrogen (p*K*a = ca. 3~5).[17a]



	3aa	4aa	5
cata. A: IPrAuCl/$AgNTf_2$	75%	21%	4%
B: $AgNTf_2$	33%	24%	40%
C: no catalyst	81%	19%	0%

Scheme 2. Initial Experiments.

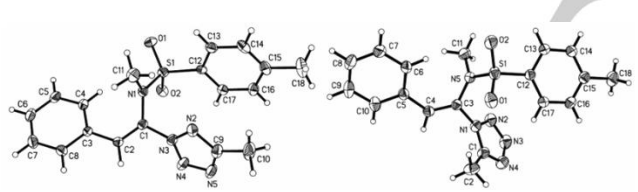
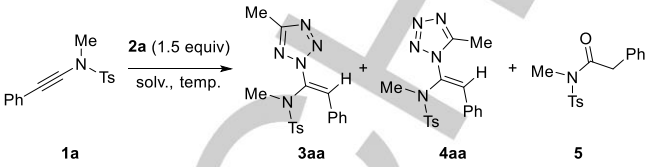


Figure 1. X-ray Structures of **3aa** (left) and **4aa** (right).

In order to further improve the ratio of **3aa** to **4aa**, various reaction conditions were screened and the results were summarized in Table 1. It can be found that the use of several solvents provided the desired adducts **3aa** and **4aa** as major products (Table 1, entries 1-5), while the DCE solvent led to the complete reaction having better result on the ratio of *N*-2 to *N*-1 adducts (1/0.23) with the absence of side product **5** (Table 1, entry 1). Next, the temperature studies indicated that the similar results were obtained when the reaction were carried out at 80 and 60 ˚C (Table 1, entries 1 *vs* 6), but the reaction needed prolonged time under low temperature conditions. Furthermore, the substrate **1a** could not be consumed completely at 40 ˚C for 12 h, even no reaction happened at ambient temperature (Table 1, entries 7 and 8). The loading of 2*H*-tetrazole **2a** was also further reduced to 1.1 equiv without obvious influence on the reaction efficiency but with more *N*-1 adduct **4aa** (Table 1, entries 9 and 10). Finally, the optimal conditions were established with DCE as the solvent at 80 ˚C in the absence of any catalyst (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions. [a]



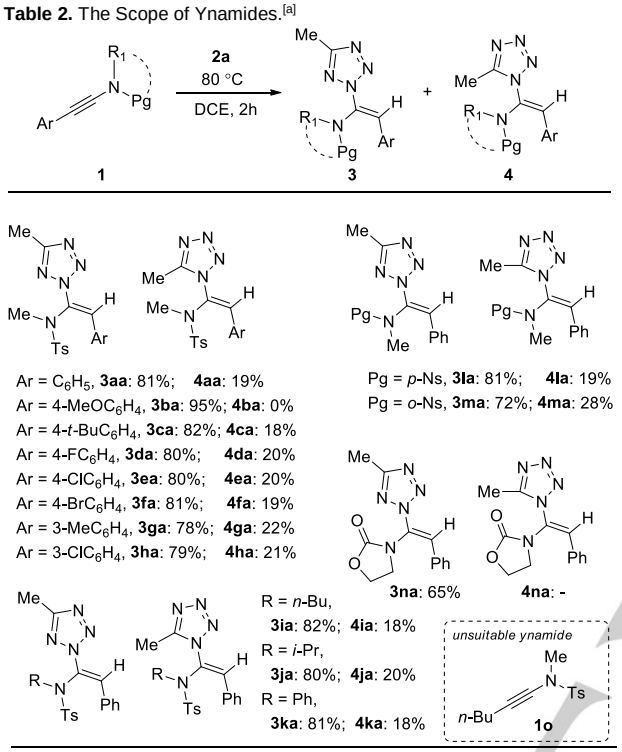
Entry	Solv.	Temp. (˚C)	Time (h)	**3aa/4aa/5/1a**[b]
1	DCE	80	2	1/0.23/0/0
2	1,4-dioxane	80	2	1/0.49/0.3/0
3	THF	80	2	1/0.71/0.02/0.14
4	toluene	80	2	1/0.27/0.15/0
5	CH_3CN	80	2	1/0.76/0.03/0.03
6	DCE	60	10	1/0.24/0/0
7	DCE	40	12	1/0.22/0/1.15
8	DCE	20	24	0
9[c]	DCE	80	2	1/0.4/0/0
10[d]	DCE	80	2	1/0.48/0/0

[a] All the reactions were carried out with ynamide **1a** (0.1 mmol), 2*H*-tetrazole **2a** (1.5 equiv) in indicated solvent (1.0 mL), unless otherwise noted. [b] The ratios were obtained by the crude ^{1}H NMR analysis. [c] 1.3 equiv of **2a** was used. [d] 1.1 equiv of **2a** was used.

Having established the optimal reaction conditions, we decided to investigate the scope of substrates. Firstly, the reactions of various ynamides (**1a**-**o**) with tetrazole **2a** were carried out and the results were summarized in Table 2. As can be seen, different aromatic alkyne-derived ynamides (**1a**-**h**) could react with **2a** efficiently; giving the desired *N*-2 adducts **3aa**-**3ha** in 78-95% yields and *N*-1 isomers **4aa**-**4ha** in 0-22% yields.[18] The electronic nature of ynamide substrates have not obvious effects on the reaction efficiencies, whereas the strong electron-donating group (MeO-) substituted ynamides (**1b**) led to the formation of *N*-2 adduct **3ba** as the only product.[19] For the ynamides (**1g**-**h**) with meta-substituents on the aromatic ring, the corresponding products (**3ga**-**ha** and **4ga**-**ha**) could be obtained in similar yields. Furthermore, the reactions of the ynamides (**1i**-**k**) having different *N*-substitutents (*n*-Bu, *i*-Pr, Ph) could proceed smoothly to provide the expected products **3ia-ka** in good yields with minor isomers **4ia-ka**. Subsequent studies showed that the protecting groups of ynamides could be changed for other sulfonyl groups (*p*-Ns, *o*-Ns) to give the desired adducts **3la**-**ma** and **4la**-**ma** with high reaction efficiency. The use of cyclic carbamate-derived ynamide **1n** under optimal conditions can achieve the synthesis of *N*-2 adduct **3na** in 65% yield with some

minor inseparable products. It should be mentioned that alkylated ynamides could be not good substrates for current transformations, thus the formation of a complex mixture was observed upon the use of substrate **1o**.

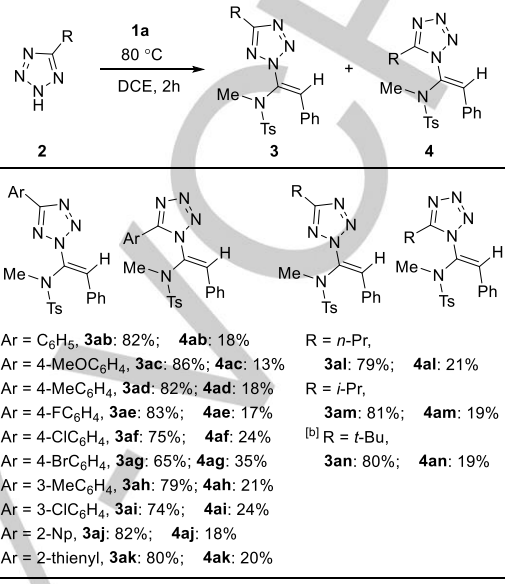
Table 2. The Scope of Ynamides.[a]



[a] All the reactions were carried out with ynamide **1** (0.3 mmol), **2a** (0.45 mmol, 1.5 equiv) in DCE (3 mL) at 80 ˚C for 2 h, and the isolated yields were provided for all products.

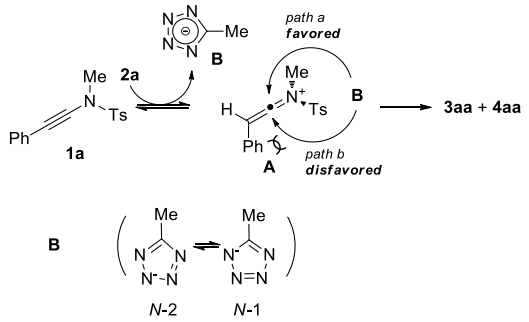
Next, the scope of tetrazoles[17] for the hydroheteroarylation reaction of ynamide **1a** was investigated. It can be found that a variety of functionalized (*Z*)-*α*-tetrazol enamides (**3ab**-**an** and **4ab**-**an**) were obtained in good yields (Table 3). Both the aryl tetrazoles (**2c**-**g**) with electron-donating groups (MeO, Me) and electron-withdrawing groups (F, Cl, Br) on the aryl ring were compatible, leading to the formation of enamide products in high efficiency. With regard to the substituents on the meta-aromatic ring were also tolerated to present transformation, and the products (**3ah**-**ai** and **4ah**-**ai**) were readily obtained in high yields. Notably, the use of 5-(naphthalen-2-yl)-2*H*-tetrazole (**2j**) could achieve the synthesis of enamides **3aj** and **4aj** in 81% and 18% yields, respectively. The 2-thienyl substituted tetrazole **2k** was also an efficient substrate for the reaction, forming the desired products without obvious changes on the yields. Besides 5-methyl-2*H*-tetrazole (**2a**), other alkylated tetrazoles (**2l**-**n**) were tested to the reaction under optimal conditions, giving the corresponding adducts efficiently albeit with different steric hindrance. Particularly, the yields of **4l**-**n** didn't decrease obviously with the introduction of bulky groups (19-21%). It should be highlighted that all the products were obtained with complete regio- and stereo-selectivities, and good chemoselectivity (ca. 3/1 ~ 4/1).

Table 3. The Scope of Tetrazoles. [a]



[a] All the reactions were carried out with ynamide **1a** (0.3 mmol), **2** (1.5 equiv) in DCE (3 mL) at 80 ˚C for 2 h, unless otherwise noted. And the isolated yields were provided for all products. [b] Reaction time is 12 h.

Based on the above experiments, a tentative mechanism for the formation of (*Z*)-*α*-tetrazol enamides **3aa** and **4aa** were proposed in Scheme 3.[4b,9] Initially, ynamide **1a** could be converted into the key reactive keteniminium intermediates **A** under acidic conditions, depending on the deprotonation of 1*H*-tetrazole **2a** along with the formation of the tetrazole anion **B**. The nucleophilic attack of anion **B** to **A** could give the two adducts (**3aa** and **4aa**) derived from different reactive sites of **B** (*N*-2 and *N*-1, respectively). It should be noted that the chemoselectivity (*N*-2 *vs* *N*-1) could depend on both polarity of solvent and nature of anion **B**,[12] and the *syn*-addition to form (*Z*)-*α*-tetrazol enamide products could be due to the two different addition paths of **B**, which is preferable from path *a* than path *b* because of the distinct sterohindrances.



Scheme 3. The Proposed Reaction Mechanism for the Formation of **3aa** and **4aa**.

Conclusions

In summary, a novel metal-free hydroheteroarylation reaction of ynamides with tetrazoles has been developed to achieve the direct synthesis of a variety of functionalized (*Z*)-*α*-tetrazol enamide products. The reaction could proceed efficiently with complete regio- and stereo-selectivities, and good chemoseletivities. It should be noted that 2*H*-tetrazoles play two key roles as the Brönsted acids and nucleophiles. The possible mechanism was proposed to be going through a key keteniminium intermediate under the acidic conditions. The features of the present transformations contain metal-free conditions, easily handled operations and high yields for the synthesis of (*Z*)-*α*-tetrazol enamides. This extra catalyst-free condition makes current reaction very advantageous for the modifications and screening of pharmaceutical products. Next works will focus on the investigations of potentially bioactive molecules and expansions of the reaction strategy.

Experimental Section

Typical procedure for the direct synthesis of (*Z*)-*α*-tetrazol enamides **3aa** and **4aa**: to a stirred solution of ynamide **1a** (85.6 mg, 0.3 mmol) in DCE (3 mL) was added 2*H*-tetrazole **2a** (37.8 mg, 0.45 mmol, 1.5 equiv) in air. The resulting mixture was placed into preheated oil bath of 80 ˚C, monitored by thin layer chromatography (TLC) analysis, generally for 2 hours. Upon the completion of reaction, the mixture was cooled to room temperature, followed by the solvent was removed by a rotary evaporator under reduced pressure. The residue was subjected to column chromatography (eluent: ethyl acetate/petrol ether = 1/10~1/3) to afford the pure *N*-2 and *N*-1 adducts (**3aa** and **4aa**), respectively.

(Z)-N,4-dimethyl-N-(1-(5-methyl-2H-tetrazol-2-yl)-2-phenylvinyl)benzenesulfonamide (**3aa**): White solid, m.p. 110.9-111.8 ˚C, yield 89.7 mg, 81%; R_f = 0.37 (hexanes/EtOAc = 3/1); **^{1}H NMR** ($CDCl_3$, *500 MHz*): δ 7.71 (dd, *J* = 7.9, 2.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.43-7.38 (m, 3H), 7.37 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 3.31 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H); **^{13}C NMR** ($CDCl_3$, *125.8 MHz*): δ 162.5, 144.1, 135.3, 131.3, 130.6, 130.0, 129.7, 129.3, 128.9, 127.3, 126.4, 37.1, 21.6, 10.8. **HRMS** (ESI) m/z calcd for $C_{18}H_{20}N_5O_2S$ $(M+H)^+$ 370.1332, found 370.1335.

(Z)-N,4-dimethyl-N-(1-(5-methyl-1H-tetrazol-1-yl)-2-phenylvinyl)benzenesulfonamide (**4aa**): White solid, m.p. 111.1-112.5 ˚C, yield 21.0 mg, 19%; R_f = 0.17 (hexanes/EtOAc = 3/1); **^{1}H NMR** ($CDCl_3$, *500 MHz*): δ 7.71 (dd, *J* = 8.1, 1.1 Hz, 2H), 7.51-7.42 (m, 3H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.45 (s, 1H), 3.19 (s, 3H), 2.77 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** ($CDCl_3$, *125.8 MHz*): δ 153.1, 146.9, 144.7, 134.3, 130.6, 130.4, 129.9, 129.22, 129.19, 127.6, 126.8, 37.0, 21.6, 9.4. **HRMS** (ESI) m/z calcd for $C_{18}H_{20}N_5O_2S$ $(M+H)^+$ 370.1332, found 370.1336.

Acknowledgments

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Keywords: Metal-free • Hydroheteroarylation • Ynamide • Tetrazole • Enamide

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[16] For crystallographic data, please see the Supporting Information. CCDC 1906,493 (**3aa**) and 1906,494 (**4aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] The structures of all products were determined by NMR spectroscopic analysis, and the (*Z*)-configurations were tentatively assigned by analogy with that of **3aa** and **4aa**.

[19] The rationale for the formation of single *syn*-hydrofunctionalization product **3ba** under current conditions is unclear to us.

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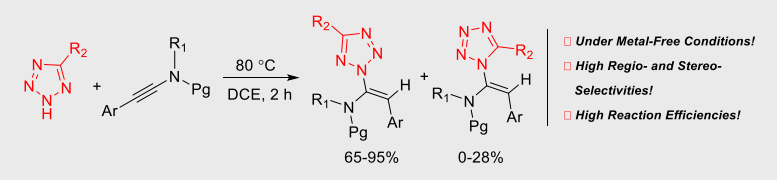

Addition Reaction

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Direct Hydroheteroarylation of Ynamides with 2*H*-Tetrazoles: Regio- and Stereo-Selective Synthesis of (*Z*)-α-Tetrazol Enamides

A reaction of ynamides with 2*H*-tetrazoles could proceed in the absence of any catalyst, providing a variety of (*Z*)-α-tetrazol enamides efficiently. The reaction could undergo a key keteniminium intermediate, leading to the formation of C-N bonds. The present reaction features simple experimental operations and mild reaction conditions, high chemo-, regio- and stereo-selectivities, and high reaction efficiencies.

- A catalyst-free reaction of ynamides with 2*H*-tetrazoles was achieved to afford (*Z*)-α-tetrazol enamides efficiently.
- The reaction could proceed in a highly regio- and stereo-selective manner.