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Tf_2NH-Catalyzed formal [3+2] cycloaddition of oxadiazolones with ynamides: a simple access to aminoimidazoles†

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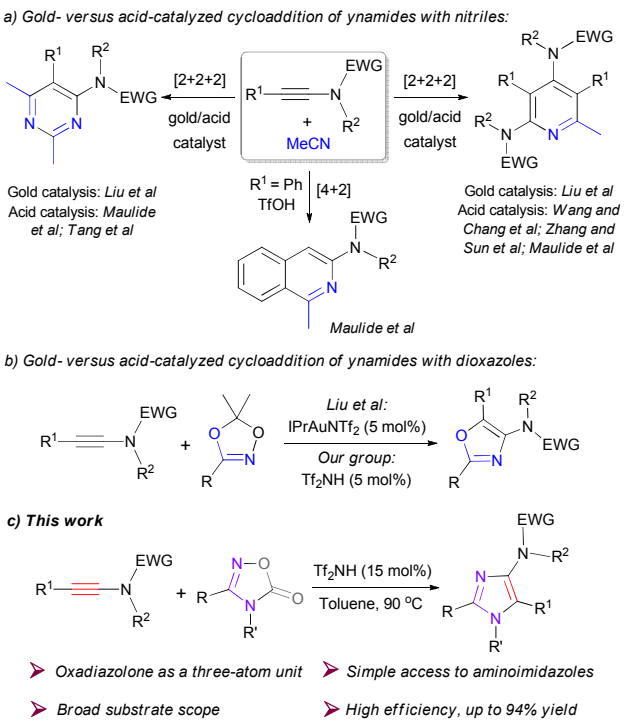
Oxadiazolones are first employed as the three-atom coupling partners in the Tf_2NH-catalyzed cycloaddition with ynamides. This formal [3+2] cycloaddition allows a rapid synthesis of aminoimidazoles with broad substrate scope. The approach also features a metal-free catalytic cycloaddition process, which may find applications in the synthesis of bioactive molecules. Besides, the resulting *N*-methyl products can further be readily converted to free N-H aminoimidazoles.

Combinations of various unsaturated building units in cycloadditions have created remarkable opportunities to construct heterocycles of high complexity. In this regard, the development of new cycloaddition partner has great significance. 1,2,4-Oxadiazol-5(4*H*)-one (abbreviated as oxadiazolone) has emerged as a versatile precursor for the synthesis of useful amidine motifs.[1] Seeking its new synthetic utility, oxadiazolone could possibly serve as a three-atom building unit in the cycloaddition process. To the best of our knowledge, the employment of oxadiazolone as a potential cycloaddition partner has never been reported before.

The cycloaddition of ynamides with various unsaturated precursors, owing to its rapid assembly of structurally complex heterocycles in a convergent and step-economical fashion, has attracted considerable attention over the past decade. Most of the reactions rely on transition-metal catalysis,[2–4] gold catalysis in particular[3,4]. For example, in 2014, Liu and co-workers developed an elegant gold-catalyzed [2+2+2] cycloaddition of ynamides with nitriles for the synthesis of pyrimidines (**Scheme 1a**).[4a] Notably, the chemoselectivity can be switched by employing terminal ynamides as the substrates, enabling an easy access to pyridine core (**Scheme 1a**).[4b] Based on these seminal works, Zhang and Sun et al,[5] Wang and Chang et al,[6] and Maulide et al[7] independently found that the similar cycloadditions toward pyridines also proceeded smoothly in the presence of acid catalysts (**Scheme 1a**). In the process, ynamide was first activated by acid catalysts to form keteniminium ion



Scheme 1. Cycloadditions of ynamides with unsaturated precursors.

intermediate, which then underwent the reactions with nitrile. Following the same strategy, pyrimidines and isoquinolines can also be constructed by varying the reaction conditions and the substituents (**Scheme 1a**).[8] Very recently, gold- and Tf_2NH-catalyzed formal [3+2] cycloadditions of ynamides with dioxazoles were developed by Liu et al[3l] and our group[9], respectively (**Scheme 1b**). Prompted by these works and our long-standing interests in exploring new cycloaddition patterns,[10] we envisaged that strong Brønsted acids could also promote the cycloaddition of oxadiazolones with ynamides. Just as anticipated, in the presence of Tf_2NH catalyst, the [3+2] cycloaddition of oxadiazolones with ynamides proceeded efficiently, enabling a facile synthesis of

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aminoimidazoles (**Scheme 1c**). It is noted that aminoimidazoles are core structures of various bioactive molecules and medically relevant compounds.[11] Their conventional synthesis often involves the palladium-catalyzed C–N cross-coupling of haloimidazoles and amines.[12] From an economical and environmental point of view, our metal-free catalytic cycloaddition is much more preferred, especially in the medicinal chemistry since the removal of the resulting metal residues can be expensive.[13] We herein present the results of our investigations.

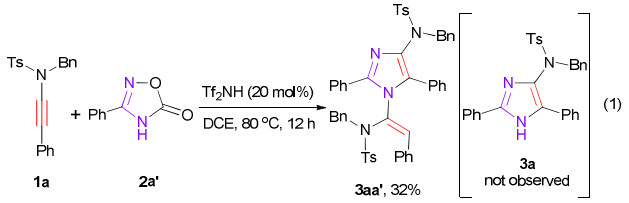
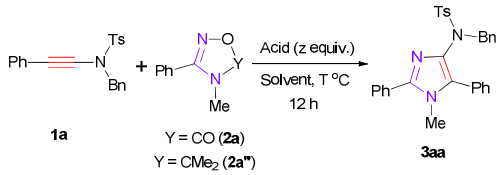


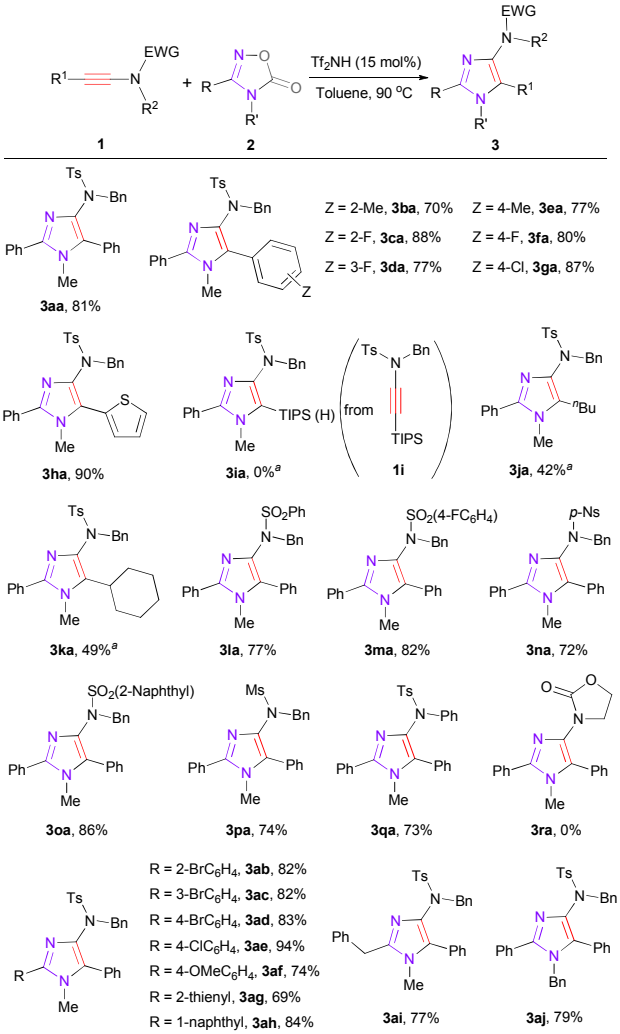
Table 1. Optimization of the reaction conditions[a]



Entry	Acid	z	Oxa-diazolone	Solvent	T (°C)	Yield of **3aa** (%)[b]
1	Tf_2NH	0.20	**2a**	DCE	80	71
2	TfOH	0.20	**2a**	DCE	80	61
3	Tf_2NH	0.15	**2a**	DCE	80	77
4	Tf_2NH	0.10	**2a**	DCE	80	67
5[c]	Tf_2NH	0.15	**2a**	DCE	80	66
6	Tf_2NH	0.15	**2a**	Toluene	80	79
7	Tf_2NH	0.15	**2a**	Toluene	60	61
8	Tf_2NH	0.15	**2a**	Toluene	90	86
9	Tf_2NH	0.15	**2a**	Toluene	100	81
10	Tf_2NH	0.15	**2a''**	Toluene	90	0
11[d]	Tf_2NH	0.15	**2a**	Toluene	90	87 (81)[e]

[a]Reaction conditions: Acid catalyst was added to a mixture of **1a** (0.1 mmol), **2a** or **2a''** (0.11 mmol), and solvent (1.0 mL), then stirred at indicated temperature for 12 h. [b]Yields were detected by HPLC using naphthalene as the internal standard. [c]6 h. [d]**1a** (0.12 mmol) and **2a** (0.10 mmol) were employed. [e]Isolated yield.

At the outset, free N-H oxadiazolone **2a'** and ynamide **1a** were selected as the model substrates to test our hypothesis. When a catalytic amount of Tf_2NH (20 mol%) was introduced to the mixture of **1a** and **2a'**, the expected cycloaddition product **3a** was not observed, while imidazole **3aa'** was obtained as the main product (Eqn 1).[14] It is because that the in situ formed N-H imidazole **3a** can further undergo the addition with ynamide **1a** in the presence of acid catalyst. To solve this problem, *N*-Me oxadiazolone **2a** was chosen as the cycloaddition partner in the process. Indeed, when the reaction of **1a** and **2a** was carried out under the same conditions, the desired aminoimidazole **3aa** was afforded in 71% yield (**Table 1**, entry 1). The utilization of TfOH as catalyst gave an inferior result (**Table 1**, entry 2). Gratifyingly, 77% yield of **3aa** was achieved in the presence of 15 mol% of Tf_2NH (**Table 1**, entry 3). However, a lower catalyst loading (10 mol%) provided **3aa** in a decreased yield (**Table 1**, entry 4). After stirring for 6 h, the substrates were not completely consumed (**Table 1**, entry 5). The yield of **3aa** increased to 79% when varying the solvent to toluene (**Table 1**, entry 6). A screen of the temperature indicates that the best result was obtained when the cycloaddition was conducted at 90 °C (**Table 1**, entries 7–9). It is noteworthy that the attempt of using oxadiazolone **2a''** as the potential partner failed (**Table 1**, entry 10). To facilitate the purification step,[15] the amount of ynamide **1a** was increased to 1.2 equivalent, by which **3aa** was isolated in 81% yield (**Table 1**, entry 11).



Scheme 2. Substrate scope. Reaction conditions: Tf_2NH (15 mol%) was added to a mixture of **1** (0.24 mmol), **2** (0.20 mmol), and toluene (2.0 mL), then stirred at 90 °C for 12 h. Isolated yields were given. [a]Tf_2NH (1.0 equiv.), 30 min.

Subsequently, we explored the scope of ynamides with the optimized conditions and the results are shown in **Scheme 2**. A variety of aromatic groups in R^1 were all tolerated in the process. The electronic nature and position of the substituents had no significant impact on the reactivity. For example, 2-Me and 2-F

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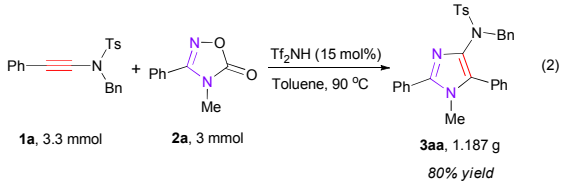
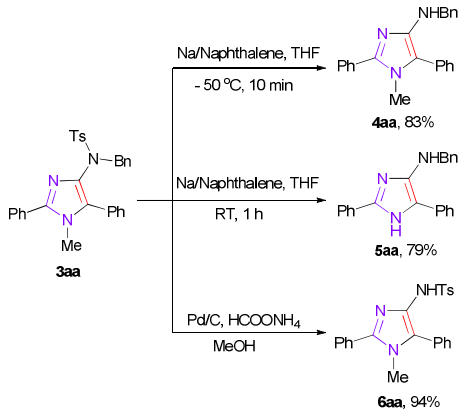
substituted ynamides could be readily converted to the corresponding imidazoles **3ba** and **3ca** in 70% and 88% yield, respectively. The *meta*- and *para*-substituents (F, Me and Cl) on the phenyl ring also gave satisfactory results (**3da–3ga**). Remarkably, the cycloaddition of 2-thienyl derived ynamide **1h** with **2a** furnished the imidazole **3ha** in an excellent yield. However, no desired product was obtained when using TIPS-derived ynamide **1i** as the substrate even in the presence of a stoichiometric amount of acid. In the cases of other alkyl groups such as *n*-butyl and cyclohexyl in R^1, 1.0 equivalent of Tf_2NH was required to achieve moderate yields (**3ja**, **3ka**) and the reactions can be finished within 30 min. The scope of the sulfonyl group on the nitrogen atom was also investigated. When Ph, *p*-FPh, and *p*-NO_2Ph were employed in the sulfonyl group, the reactions proceeded smoothly, providing the corresponding aminoimidazoles **3la–3na** in good yields. Besides, sterically hindered 2-naphthylsulfonyl substituted ynamide **1o** underwent the process with a high efficiency. The methylsulfonyl group on the nitrogen atom was tolerated as well, producing **3pa** in 74% yield. Gratifyingly, submitting *N*-Ph ynamide **1q** to the standard conditions delivered the desired imidazole **3qa** in 73% yield. Disappointedly, the more electron-rich ynamide **1r** bearing an oxazolidine group cannot participate in the reaction because of its relatively low reactivity.

Furthermore, oxadiazolones with different substituents were surveyed. 2-Br, 3-Br, and 4-Br on the phenyl ring in R were all compatible with the process, leading to the formation of imidazoles **3ab–3ad** in good yields. The electron-withdrawing substituents such as 4-Br and 4-Cl gave good results (**3ad**, **3ae**), while the electron-donating group 4-OMe afforded the product **3af** in a moderate yield (74%). 2-Thienyl was also tolerated in the reaction albeit with a slightly decreased yield (**3ag**). Notably, 84% yield of **3ah** was achieved when sterically hindered 1-naphthyl was employed. The benzyl-substituted oxadiazolone **2i** could also undergo the cycloaddition with **1a**, generating **3ai** in 77% yield. When the methyl group on the nitrogen atom was changed to benzyl, the cycloaddition proceeded efficiently as well (**3aj**).



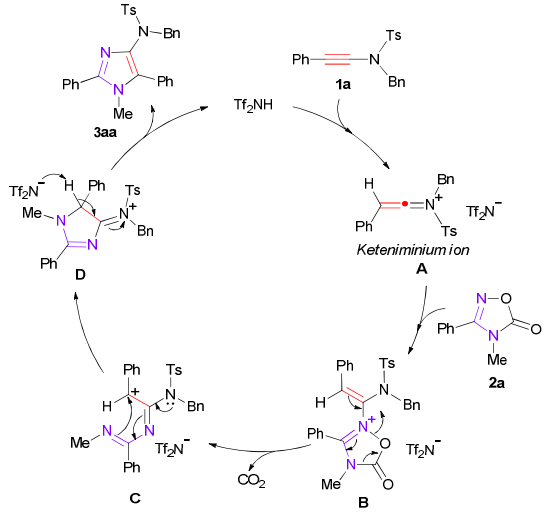
To illustrate the practicability of this approach, a gram-scale experiment was performed (Eqn 2). Ynamide **1a** (3.3 mmol) and oxadiazolone **2a** (3.0 mmol) were dissolved in 30 mL toluene. Then 15 mol% of Tf_2NH was introduced and the mixture was stirred at 90 ^oC for 12 h. The reaction was quenched by Et_3N solution (10 vol.% in pentane) and extracted with ethyl acetate. Removal of the solvent and purification by column chromatography afforded imidazole **3aa** in 80% yield (1.187 g).

Given the prevalence of aminoimidazoles in the core of bioactive molecules, the synthetic transformations of the product were further studied (**Scheme 3**). The tosyl group on the nitrogen atom of **3aa** could be easily removed by a treatment with Na/naphthalene at -50 ^oC. Surprisingly, it is found that the methyl substituent on the core ring was removed as well, producing the free N-H imidazole **5aa** with a high efficiency, when the reaction was conducted at room temperature for 1 h. This reaction provided a mild alternative for the removal of methyl protecting group. Besides, subjecting **3aa** to a mixture of Pd/C, $HCOONH_4$ and MeOH resulted in the formation of debenzylated product **6aa** in 94% yield.



Scheme 3. Further transformations of the product.

According to those works on the acid-catalyzed cycloaddition of ynamides with nitriles,[5–8] a plausible mechanism was proposed in **Scheme 4**. Initially, ynamide **1a** is protonated by Tf_2NH to generate keteniminium ion **A**.[16] Then, a nucleophilic attack of oxadiazolone **2a** on the intermediate **A** forms the adduct **B**, which undergoes ring fragmentation to eliminate one molecule of CO_2, resulting in the formation of benzylic carbocation **C**. A subsequent intramolecular cyclization of **C** furnishes the iminium ion intermediate **D**. Finally, deprotonation of **D** affords the imidazole **3aa** and regenerates the acid catalyst. It is noted that the substrate scope supports this cationic-type mechanism. The annulations of alkyl-derived ynamides with oxadiazolone **2a** afforded the products in low yields, while the aryl-substituted substrates gave good results. Because the benzylic cation in intermediate **C** (aryl groups) is more stable than alkyl carbocation (alkyl groups).



Scheme 4. Proposed mechanism.

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In conclusion, we have developed a formal [3+2] approach to access aminoimidazoles through the Tf_2NH-catalyzed cycloaddition of oxadiazolones with ynamides, in which oxadiazolones are first employed as the three-atom building units. The approach also features a metal-free catalytic cycloaddition process, broad substrate scope, and high efficiency. Besides, the *N*-methyl products can be readily converted to free N-H aminoimidazoles. We believe that this metal-free catalytic cycloaddition will have potential applications in the medicinal chemistry.

Acknowledgements

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