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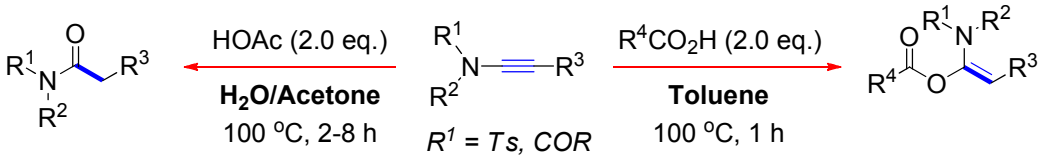
Graphical Abstract



Metal-free, Solvent-controlled, Chemoselective

Metal-Free Hydroacyloxylation and Hydration Reactions of Ynamides: Synthesis α-Acyloxyenamides and *N*-Acylsulfonamides

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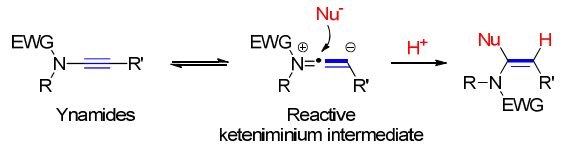
Two types of highly efficient and operation-simple reactions of ynamides under metal-free conditions have been developed, including hydroacyloxylation and hydration, which afforded highly functionalized α-acyloxyenamides and pharmaceutically important *N*-acylsulfonamides in good to excellent yields.

Ynamides are a class of electron-deficient ynamines with an initial report dating far back to the pioneering work of Viehe in 1972.[1] Substitution of a nitrogen atom for electronegative elements, such as acyl, sulfonyl groups, has realized an exceptionally fine balance between stability and reactivity of ynamines, thus providing a workable solution to the long-term problem of the sensitivity of these compounds toward hydrolysis.[2] In the past decade, explorations on the synthetic utility of ynamides captivated the attention of the scientific community and hence resulted in a great number of transformations.[3] Among these, the regioselective addition of a nucleophilic moiety to the reactive keteniminium intermediates, generated from ynamides due to the electron-donating ability of the nitrogen, constitutes an attractive strategy to prepare the functionalized enamides.[4] However, this strategy remains largely underexploited, especially under metal-free conditions.



The transition-metal-catalyzed hydroacyloxylation reaction of alkynes with carboxylic acids is a straightforward approach to synthetically valuable enol esters.[5] Recently, Lam and co-workers reported a palladium-catalyzed regio- and stereoselective addition of carboxylic acids to ynamides affording the α-acyloxyenamides (Figure 1).[6] To our knowledge, this is the only known report to date regarding the hydroacyloxylation reaction of ynamides.[7] *N*-Acylsulfonamides are also an important structural motif prevalent in a wide range of pharmaceutically active compounds, such as antibacterial inhibitors for tRNA synthetase, therapeutic agents for Alzheimer's disease, and antagonists for Angiotensin II.[8] Even though a number of synthetic methods are available,[9] the development of novel and convenient methods is still of great value. The hydrolysis of ynamides could be an ideal pathway to synthesize *N*-acylsulfonamides due to recent breakthroughs in the preparation of these substrates.[10] However, only a limited number of cases for such hydrolysis are available in the literature (Figure 1),[11] probably due to the intentionally avoidance of this kind of transformation and hence resulting in the ignorance of their synthetically value. As our ongoing efforts to develop novel organic reactions by employing functionalized alkynes,[12] we herein wish to report two types of highly efficient metal-free transformations of ynamides, hydroacyloxylation and hydration, which provide practical and operation-simple methods for the divergent synthesis of synthetically useful α-acyloxyenamides[13] and pharmaceutically important *N*-acylsulfonamides in both high yields and high efficiency (Figure 1).

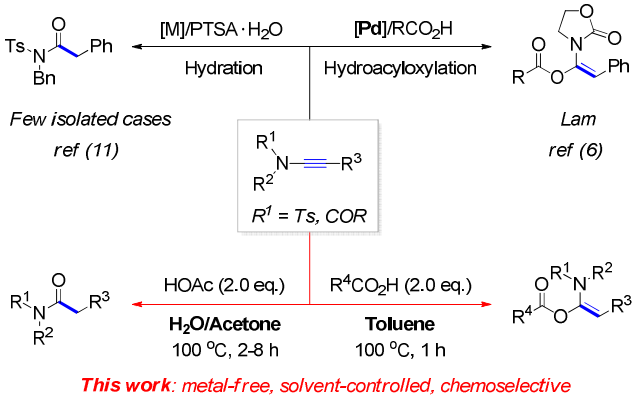
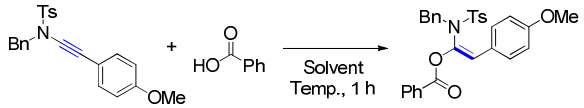


Figure 1 Hydroacyloxylation and hydration reactions of ynamides

Table 1 Optimization of the reaction conditions.[a]



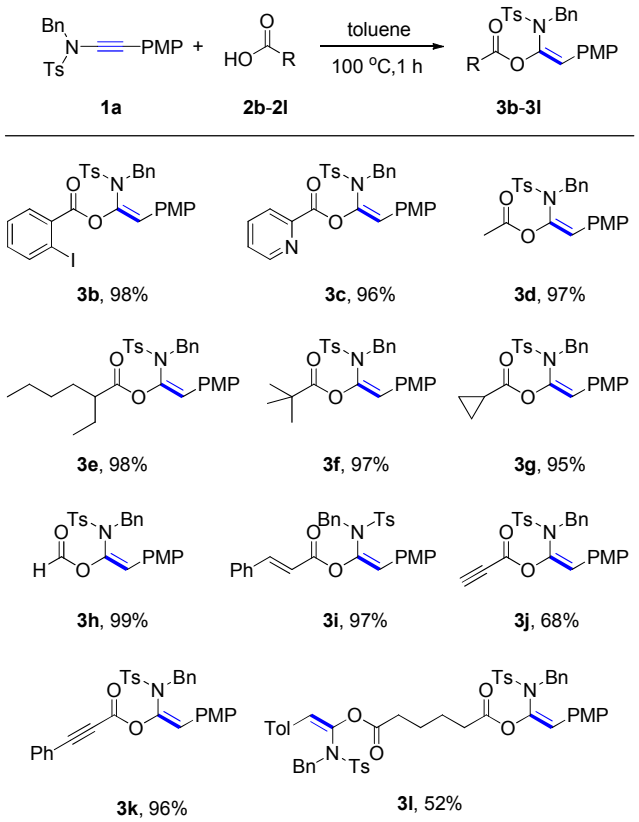
1a **2a** **3a**

Entry	*T* (ºC)	Solvent	Yield (%)[b]
1	20	toluene	25
2	80	toluene	60
3	100	toluene	98
4	120	toluene	85
5	100	DMF	0
6	100	DMSO	0
7	100	1,4-dioxane	0

[a] Reactions were performed on a 0.2 mmol scale of **1a** and a 0.3 mmol scale of **2a** in 1.0 mL solvent. [b] Isolated yields.

Initially, the reaction of ynamide (**1a**) with benzoic acid (**2a**) was selected as model for optimization of the reaction conditions (Table 1). Effect of the reaction temperature was first examined using toluene as the solvent for a reaction period of 1 hour. Delightfully, the desired product, α-acyloxyenamide **3a**, was

obtained in 25% yield at room temperature (*ca*. 20 °C) in toluene (Table 1, entry 1). Encouraged by this promising result, the reaction temperature was increased gradually, and a nearly quantitative yield (98%) was obtained at 100 °C (Table 1, entries 2 and 3). However, as the temperature was increased to 120 °C, the ynamide yield decreased to 85% (Table 1, entry 4). Notably, the hydroacyloxylation of benzoic acid **2a** with ynamide **1a** was regio- and stereoselective. The structure of product **3a** was established by comparing its $^{1}H/^{13}C$ NMR spectra to those of similar compounds reported by Lam and co-workers.[6] Next, we evaluated the solvent effect at a fixed temperature of 100 °C. Surprisingly, no reactions took place when solvents such as DMF, DMSO, and 1,4-dioxane were used (Table 1, entries 5, 6, and 7). Therefore, the reaction conditions listed in entry 3 were found to be optimal and selected for further investigations.



Scheme 1 Scope of carboxylic acids in the hydroacyloxylation of ynamides. PMP = 4-Methoxyphenyl.

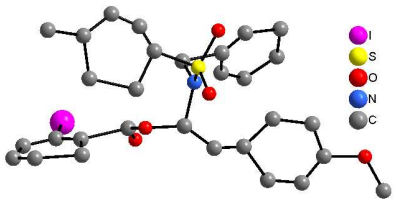
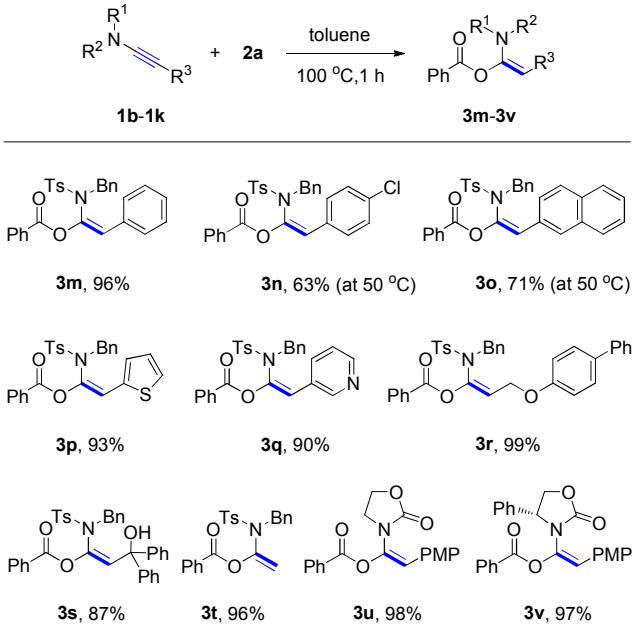


Figure 2 Single crystal structure of **3b**.

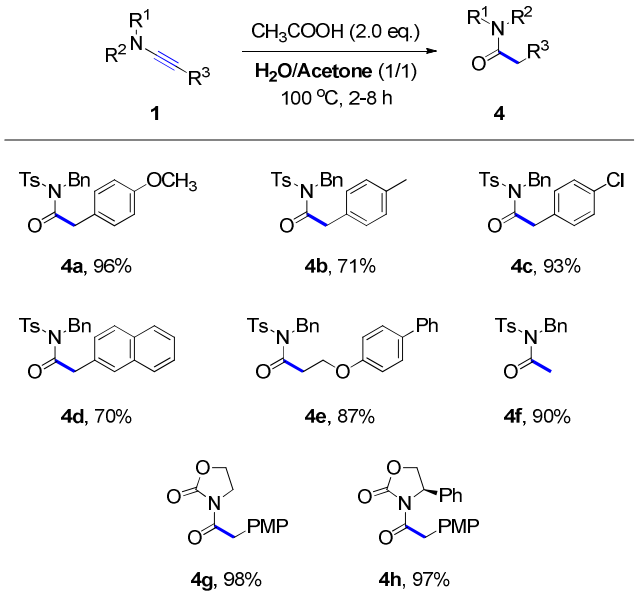
With the optimized reaction conditions in hand (100 °C in toluene), the substrate scope of the metal-free hydroacyloxylation reaction was next investigated using diverse carboxlic acids with different substitution patterns. The experimental results from these studies are summarized in Scheme 1. In general, all reactions proceeded smoothly affording the corresponding α-acyloxyenamides (**3b**–**3l**) in good to excellent yields (52–99%) with high level regio- and stereo-control. The stereochemistry of α-acyloxyenamides was further unambiguously confirmed by the X-ray diffraction (XRD) analysis of product **3b** (CCDC 1010978) (Figure 2). A possible rationalization of this high stereoselectivity might be attributed to the steric repulsion in the transition state and the stability of *E*-configuration product. The scope of carboxylic acids adaptability to the hydroacyloxylation reaction with ynamides was quite broad. For example, the aromatic carboxylic acids such as 2-iodobenzoic acid (**2b**) and picolinic acid (**2c**) efficiently reacted with ynamide **1a** to afford the desired products **3b** and **3c** in 98 and 96% yields, respectively. Similarly, a broad scope of aliphatic carboxylic acids, including diverse alkyl, alkenyl, and alkynyl carboxylic acids, could be applied to this hydroacyloxylation reaction with ynamide **1a**, allowing the synthesis of functionalized α-acyloxyenamides (**3d**–**3l**). It is noteworthy that the reaction of ynamide **1a** with formic acid (**2h**), the simplest carboxylic acid, afforded the corresponding product **3h** in nearly quantative yield (99%). In addition, the presence of functional groups, such as cyclopropyl (**3g**), alkenyl (**3i**), and alkynyl (**3j** and **3k**), was well tolerated, thus providing a group of synthetically valuable intermediates. Furthermore, the bis-α-acyloxyenamide **3l** could be synthesized in a moderate yield (52%) through the one-step reaction with 0.5 equivalent amount of adipic acid.



Scheme 2 Scope of ynamides in the hydroacyloxylation of ynamides. PMP = 4-Methoxyphenyl.

Following illustration of the compartibility of ynamide **1a** to a broad variety of carboxylic acids, investigation was furthered on the scope of the ynamides and the experimental results summarized in Scheme 2. The R^3 group of ynamides was first systemically varied. We were pleased to find that aryl- (*e.g.*, phenyl, 4-chlorophenyl), fused aryl- (*e.g.*,

naphthyl), and heteroaryl- (*e.g.*, 2-thienyl, 3-pyridyl) substituted ynamides were all suitable substrates for the hydroacyloxylation, affording the corresponding α-acyloxyenamides (**3m**–**3q**) in 63–96% yields. The aliphatic R^3 group containing functionalities such as ether, hydroxyl group has no influence on the reaction outcome. In each case, the functionalized α-acyloxyenamides **3r** and **3s** were obtained in 99% and 87% yields. Notably, when the ynamide **1i** that had a terminal alkyne unit (R^3 = H) was subjected to the reaction with benzoic acid under the standard conditions, the desired product **3t** was obtained in 96% yield. Further, the electron-withdrawing group on the nitrogen center of ynamides was varied. For example, oxazolidinone-substituted ynamides **1j** and **1k** were found to be effective substrates, providing products **3u** and **3v** in 98% and 97% yields.



Scheme 3 Hydration reaction of ynamides to *N*-acylsulfonamides. PMP = 4-Methoxyphenyl.

Due to the biological and pharmaceutical importance of *N*-acylsulfonamides[8] as well as the lack of a systemical study on the hydration of ynamides,[3] we next focused on the search for the conditions of the hydrolysis of ynamides. After several trials, we ultimately realized that, with two equivalent amounts of acetic acid in H_2O and acetone as mixture solvent can offer a clean and complete conversion from ynamides to *N*-acylsulfonamides. Some selected results are shown in Scheme 3. This hydration reaction of ynamides all smoothly proceeded and afforded the corresponding *N*-acylsulfonamides (**4a**–**4f**) in 70–96% yields. In addition, the variation of *N*-substituents has no influence on the reaction outcome, for example, imides **4g** and **4h** were obtained in excellent yields under the hydrolysis conditions. Consequently, an efficient and operation-simple access to pharmaceutically important *N*-acylsulfonamides was developed. Notably, for most reactions listed in Schemes 1, 2, and 3, the pure products can be obtained simply by filtrating the reaction mixture, without the need of tedious chromatographic purification steps.

In summary, we have developed two types of highly efficient metal-free reactions of ynamides, hydroacyloxylation and hydration reactions, which afforded a variety of highly functionalized α-acyloxyenamides and pharmaceutically important *N*-acylsulfonamides in good to excellent yields.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, and spectra copies of all compounds. See DOI: 10.1039/b000000x/

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